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POLYMER RESIN FORMULATION HAVING ANTI-MICROBIAL OR

ANTI-COAGULABILITY AND PREPARATION METHOD THEREOF

BACKGROUND OF THE INVENTION

(a) Field of the Invention

5 The present invention relates to a method for preparing an anti-
microbial or anti-coagulating polymer resin, particularly to a method for
preparing a functional polymer resin that can prevent secondary bacterial
infection, inhibit coagulation of blood when inserted into a human body,
and maintain superior medicinal efficacy durability even after injection and
10 extrusion molding, by combining a material that is safe to a human body,
has superior compatibility with materials for commonly used medical
instruments/appliances, and has superior anti-microbial or anti-coagulating
properties on the surface of a product, with various materials for medical
instruments/appliances such as silicon, etc., in a non-solvent form.

15 **(b) Description of the Related Art**

Various forms of organic anti-microbial formulations for
conventional anti-microbial and anti-pollutant functions such as quaternary
ammonium salt, chlorohexidine, carbendazim, thiazole, azole, Sn types,
etc. have been reported. However, many of the anti-microbial and anti-
20 pollutant products using the above materials have problems including
unsecured safety due to toxicity, and ecosystem destruction due to release
of environmental hormones. Additionally, their anti-microbial effects may
be decreased due to thermal decomposition during high temperature
processing, and product deterioration due to yellowing may also occur.
25 Particularly, a polymer resin used in the medical field such as for an

artificial blood vessel, an artificial heart, an artificial bone, artificial skin, etc. should be secured safety to a human body, and they should be protected from various pathogenic bacteria. However, anti-microbial materials of the prior art cannot completely satisfy these requirements.

5 Conventional technologies for inhibiting bacterial infection of medical instruments/appliances have been disclosed in various publications. As examples, US Patent No. 6,342,250 has disclosed a technology for coating a pharmaceutically active material on a polymer surface; US Patent No. 5,019,283 has disclosed a technology for coating a
10 pharmaceutically active material selected from Ag and an anti-microbial composition on a polymer surface; and US Patent No. 5,902,283 has disclosed a technology for coating a pharmaceutically active material such as rifamycin, penicillin, ciprofloxacin, etc. on the surface of a catheter.

 According to the above-mentioned conventional technologies, an
15 anti-microbial material is coated on a surface by an additional process after preparing a product, and drugs are eluted by DDS (Drug Delivery System) to exhibit surface anti-microbial efficacy. However, they have disadvantages including process workability, durability and effect durability, toxic problems due to remaining materials that are excessively eluted in the
20 body, and formation of volatile organic compounds (V.O.C) due to the use of an organic solvent for coating.

 In addition, when medical instruments/appliances are inserted into a human body, they react in the following way with blood to cause blood coagulation. Firstly, plasma proteins such as fibrinogen, albumin gamma-globulin, etc. are absorbed into the medical instruments/appliances. After
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a protein such as fibrinogen, which causes formation of thromboses, is absorbed, adhesion of blood platelets begins to cause more adhesion and coagulation of blood platelets to form thromboses. Simultaneously, a blood coagulation system is operated as blood coagulation factors are activated, and finally thrombin activates fibrinogen into fibrin to coagulate fibrin, thereby generating blood coagulation.

In order to solve these blood coagulation problems, studies on technologies for preventing blood coagulation by medical instruments/appliances (e.g., catheters, stents, artificial bone, artificial articulation) are under progress. As examples, as a method for preventing formation of thromboses by inhibiting adhesion of blood platelets, a method of using albumin is known (MA Packham, G Evans, MF Glynn, and JF Mustard, The effects of plasma proteins on the interaction of platelet with glass surfaces, J. Lab. Clin. Med., 73: 686-97, 1969; GH Ryu. Dk Han, YH Kim, and BG Min, Albumin immobilized polyurethane and its blood compatibility, Trans. Am. Soc. Artif. Int. Organs, 38: 644-648, 1992). Additionally, as a method for inhibiting formation of thromboses by inactivation of a coagulation factor, a method of combining heparin anticoagulant with a living body material is disclosed in EP 0 294 905 1A; and a method of treating heparin and polyethyleneoxide together is disclosed in EP 0081 853 A1. However, since these methods also use coating of anti-coagulants on an external surface, they cannot overcome the above-mentioned disadvantages of conventional bacterial infection inhibition technologies.

SUMMARY OF THE INVENTION

In order to solve these problems of the prior art, it is an object of the present invention to provide a method for preparing an anti-microbial or anti-coagulating polymer resin that can be easily prepared and has superior durability and compatibility by combining at least one kind of anti-microbial or anti-coagulating material, of which safety to a human body is secured, with a polymer resin in a non-solvent form without using a solvent.

It is another object of the present invention to provide a polymer resin prepared by the above method, which has superior compatibility with polymers and exhibits superior anti-microbial or anti-coagulating properties without being thermally decomposed even after molding processing, and thus can be extensively used for a medical polymer resin, natural rubber, petrochemical product, etc.

It is another object of the present invention to provide an anti-microbial or anti-coagulating polymer resin that can maintain a released amount of pharmaceutically active material at an appropriate level to solve the problem of toxicity by elution, and that can be extensively used for medical instruments/appliances which increase durability of pharmaceutical effects and do not comprise environmental hormones.

It is another object of the present invention to provide a method for preparing an anti-microbial or anti-coagulating medical instrument comprising the steps of mixing a polymer resin with a pharmaceutically active material under a non-solvent condition, and molding the mixture.

It is another object of the present invention to provide a method for preparing a household appliance or industrial appliance such as a food

packaging film, a food container, a water-purifying apparatus, a drinking water tank, a laundry bath, a refrigerator, etc., or a master batch (M/B) or compound.

It is another object of the present invention to provide a medical
5 instrument/appliance prepared using the above medical polymer resin.

In order to achieve these objects, the present invention provides a method for preparing an anti-microbial or anti-coagulating polymer resin, which method comprises the steps of mixing a polymer resin with at least one kind of pharmaceutically active material under a non-solvent condition.

10 The present invention also provides an anti-microbial or anti-coagulating medical polymer resin prepared by the above method, which has a maximum release concentration of pharmaceutically active materials of 10 ppm/100 hours in an aqueous solution.

The present invention also provides a method for preparing an
15 anti-microbial or anti-coagulating medical instrument/appliance, which method comprises the steps of a) mixing a polymer resin with at least one kind of pharmaceutically active material under a non-solvent condition; and b) molding and processing the mixture.

Preferably, the method for preparing a medical
20 instrument/appliance comprises the step of mixing a silicon resin with a pharmaceutically active material and conducting physical molding and processing at 450 to 600 °C for 5 seconds under a non-solvent condition to prepare a silicon catheter.

In addition, the present invention also provides a method for
25 preparing a master batch or compound, which method comprises the steps

of mixing a resin selected from a group consisting of linear low density polyethylene (LLDPE), polypropylene (PP), polyethylene (PE), acrylonitrile-butadiene-styrene (ABS) copolymer, polycarbonate (PC), polystyrene (PS), and polyvinylchloride (PVC), with at least one kind of pharmaceutically
5 active material, and molding and processing at 100 to 300 °C under a non-solvent condition.

The present invention also provides an anti-microbial or anti-coagulating medical appliance prepared by the above method.

The present invention also provides an anti-microbial or anti-
10 coagulating master batch or compound prepared by the above method.

The anti-microbial or anti-coagulating master batch can be used for preparing medical appliances, household appliances, industrial appliances, petrochemical appliances, etc.

The present invention also provides a method for preparing a paint,
15 which method comprises the steps of mixing an anti-microbial material selected from a group consisting of grepafloxacin, sparfloxacin, clinafloxacin, enoxacin, leme-floxacin, norfloxacin, pipemidic acid, ciprofloxacin, temafloxacin, tosufloxacin, ketoconazole, itraconazole, econazole, isoconazole, fluconazole, miconazole, terbinafine, and a salt
20 thereof, with one or more kinds of polymer resin selected from a group consisting of alkyd resin, acryl resin, urethane resin, epoxy resin, phenol resin, urea resin, melamine resin, and a modified resin thereof.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention will now be explained in more detail.

25 The present invention provides a method for preparing a polymer

resin that has superior compatibility with commonly-used polymer resins and medical materials and has superior anti-microbial or anti-coagulating properties, and a polymer resin prepared by the method. The polymer resin having anti-microbial or anti-coagulating properties prepared by the method of the present invention can be used for medical appliances, household appliances, industrial appliances, petrochemical appliances, etc., and preferably for medical appliances.

Since the polymer resin prepared by the method of the present invention is of a non-solvent form as opposed to the conventional resins prepared with solvent, it can maintain pharmaceutical activity even if molded at a high temperature, it has industrial advantages in terms of production cost reduction and environmental favorableness, etc., and it can maintain a release concentration of pharmaceutically active materials at an appropriate level.

In addition, the method of the present invention can solve problems of a decrease in durability due to separation and adhesion of a surface coating film due to free flexibility of main material resins, and toxicity due to excessive drug amounts remaining in a body due to a drug delivery system at the surface thereof. Additionally, the method of the present invention can overcome problems of thermal decomposition of anti-microbial or anti-coagulating materials during high temperature processing, and thus the polymer resin of the present invention can be used for essential materials and products of the medical field because it can prevent yellowing of medical instruments/appliances and inhibit bacterial infection and blood coagulation when inserted into a human body.

The polymer resin prepared according to the present invention has a maximum release speed of anti-microbial materials of 10 ppm/100 hrs, and preferably a maximum speed of 5 ppm/100 hrs.

The anti-microbial or anti-coagulating polymer resin of the present invention comprises commonly used polymer resin and at least one kind of pharmaceutically active material.

The pharmaceutically active material is preferably selected from a group consisting of anti-microbials, anti-coagulants and a mixture thereof.

As the anti-microbial, materials known to be safe to a human body can be used. The anti-microbial, which has sterilizing effects or microorganism growth-inhibiting effects against bacteria or mold, includes an anti-microbial agent and an anti-fungi and anti-pollutant agent, and anti-microbial, anti-fungi, and anti-pollution effects can be expected by the combined use thereof.

The anti-microbial agent is preferably selected from a group consisting of grepafloxacin, sparfloxacin, clinafloxacin, enoxacin, lemeefloxacin, norfloxacin, pipemidic acid, ciprofloxacin, temafloxacin, tosufloxacin, a salt thereof, and a mixture thereof.

The anti-microbial agent is preferably contained in the anti-microbial polymer resin of the present invention in an amount of 0.1 to 30 wt%, more preferably in an amount of 1 to 10 wt%. If the content of the anti-microbial agent is less than 0.1 wt%, the anti-microbial effect is slight, and if it exceeds 30 wt%, the improvement effect is not significant thus making it uneconomical.

The anti-fungi or anti-pollutant agent is preferably selected from a

group consisting of ketoconazole, fluconazole, itraconazole, econazole, miconazole, isoconazole, terbinafin, a salt thereof, and a mixture thereof.

The anti-fungi or anti-pollutant agent is preferably contained in the polymer resin of the present invention in an amount of 0.1 to 30 wt%. If
5 the content is less than 0.1 wt%, the anti-fungi effect is slight, and if it exceeds 30 wt%, the improvement effect is not significant thus making it uneconomical.

The anti-coagulant, which prevents coagulation of blood, is selected from a group consisting of warfarin, aspirin, ticlopidine, triflusal,
10 clopidogrel, cilostazol, a salt thereof, and a mixture thereof.

The anti-coagulant is preferably contained in the anti-coagulating polymer resin in an amount of 0.1 to 20 wt%, and more preferably 1 to 10 wt%. If the content is less than 0.1 wt%, the pharmaceutical effect is slight, and if it exceeds 20 wt%, the improvement effect is not significant
15 thus making it uneconomical.

The polymer resin is preferably used for a medical instrument or medical appliance, and any material that is safe and does not cause side effects can be used.

As the commonly used polymer resin, silicon resin, ABS, SAN, or
20 LLDPE is preferably used. In addition, one or more kinds selected from a group consisting of polyetherimide (PEI), polyethylene (PE), polypropylene (PP), polycarbonate (PC), polyvinylchloride (PVC), polystyrene (PS), epoxy resin, polytetrafluoroethylene (PTFE), polyacetal (POM), polyamide (PA), polyurethane (PU), ethylene-vinylacetate copolymer (EVA),
25 polymethylmethacrylate (PMMA), polyvinylalcohol (PVA), low density

polyethylene (LDPE), high density polyethylene (HDPE), polyacrylonitrile, polybutadiene, polyacrylic acid, polyacrylimide, polysulfone, polyamide-imide, polyneoprene, polydimethylsiloxane, polyetheretherketone, polyphenylenesulfide, polyvinylfluoride, polyvinylacetate, polyvinylidene fluoride, polyethersulfone, polycaprolactone (PCL), and a copolymer thereof; natural rubber; and a synthetic rubber can also be used.

Among these, a medical polymer resin is preferably selected from a group consisting of polyethylene (PE), polypropylene (PP), polycarbonate (PC), polyvinylchloride (PVC), polystyrene (PS), epoxy resin, polytetrafluoroethylene (PTFE), polyacetal (POM), polyamide (PA), polyurethane (PU), ethylene-vinylacetate copolymer (EVA), polymethylmethacrylate (PMMA), polyvinylalcohol (PVA), polycaprolactone (PCL), and a copolymer thereof; silicon resin; natural rubber; and a synthetic rubber.

In addition, the method for preparing a polymer resin of the present invention may further comprise the step of adding one or more kinds of additives selected from a group consisting of an antioxidant, a heat-stabilizer, a dispersant, and a lubricant, which are commonly used in plastic molding processing. Preferably, a dispersant and an antioxidant are also added.

The dispersant functions for uniformly dispersing commonly used resin and pharmaceutically active material. The examples include N,N'-ethylene-bis-stearamide (E.B.S.), low density polyethylene wax, etc., and they can be used alone or in combination. If used, the E.B.S. functions as a lubricant. The content of the dispersant is preferably 0.1 to 15 wt% of

the total composition. If the content is less than 0.1 wt%, dispersion is slight, and if it exceeds 15 wt%, a further effect improvement cannot be expected.

The antioxidant is used for preventing and inhibiting product
5 deterioration such as discoloration due to oxygen in the air. Examples thereof include 2,6-di-tert-butyl-p-cresol, n-octadecyl-3-(4-hydroxy-3-m-
ditert-butylphenyl)propionate, tetrakis[methylene-3-(3,5-di-tert-butyl-4-
hydroxyphenyl)propionate]methane, 1,3,5-trimethyl-2,4,6-tris-(3,5-di-t-
butyl-4-hydroxybenzene)benzene, etc. The content of the antioxidant is
10 preferably 0.1 to 2.5 wt% of the total composition. If the content is less than 0.1 wt%, the anti-oxidation effect is slight, and if it exceeds 2.5 wt%, a further effect improvement cannot be expected.

The heat-stabilizer is used for aiding maintenance of physical and chemical properties of the resin during usage of the final product, and
15 prevention of thermal degeneration during processing. As the heat-stabilizer, zinc stearate $[Zn(C_{17}H_{35}COO)_2]$, magnesium stearate $[Mg(C_{17}H_{35}COO)_2]$, barium stearate $[Ba(C_{17}H_{35}COO)_2]$, etc. can be used. The content of the heat stabilizer is preferably 0.1 to 3.5 wt% of the total composition. If the content is less than 0.1 wt%, the heat stabilizing
20 effect is slight, and if it exceeds 3.5 wt%, a further effect improvement cannot be expected.

In addition, according to the present invention, a medical instrument/appliance can be prepared using the medical polymer resin. The medical instrument/appliance is preferably a medical catheter, a
25 prosthetic hand, a prosthetic foot, an artificial bone, an artificial articulation,

artificial skin, an artificial kidney, a syringe, a blood transfusion pack, or an artificial tooth, and more preferably a silicon catheter, a prosthetic hand or a prosthetic foot. In addition, according to the present invention, a master batch or compound can be prepared using the medical polymer resin.

- 5 The master batch or compound can be used as a high functional additive in processing of industrial appliances such as food packaging material, plastic, etc., and the added amount is preferably 0.1 to 30 wt%.

The silicon catheter can be prepared by mixing a silicon resin and pharmaceutically active material, and molding and processing the mixture
10 under a non-solvent condition. Additionally, even if molding is conducted at a high temperature of 450 to 600 °C/5 sec, pharmaceutical activity can be maintained.

In addition, in case an acrylonitrile-butadiene-styrene (ABS) or styrene-acrylonitrile (SAN) resin is used, a medical polymer resin that
15 maintains pharmaceutical activity and has a low release concentration of pharmaceutically active material can be prepared by mixing the ABS or SAN resin with a pharmaceutically active material and then molding the mixture at 210 to 260°C.

In addition, in case a linear low density polyethylene resin (LLDPE)
20 is used, a medical master batch or compound that has identical or superior pharmaceutical activity to the existing one and has a remarkably low release speed of a pharmaceutically active material can be prepared by mixing the LLDPE with a pharmaceutically active material and molding the mixture at 170 to 210 °C.

25 In addition, according to the present invention, the petrochemical

or household appliance selected from a group consisting of a water-purifying apparatus, a food packing film, a food container, a refrigerator, a washing machine, a computer and peripheral device, a drinking water tank, a water tub, a bidet nozzle and a toilet cover, a desk and chair, an automobile handle, infant goods, a bathtub, and a cosmetic container can be prepared using the master batch or compound prepared by the above method.

Since the method for preparing a medical appliance of the present invention conducts molding under a non-solvent condition, an anti-microbial or anti-coagulating medical instrument or medical appliance, or a master batch or compound can be provided by a very simple method. The anti-microbial or anti-coagulating medical instrument or appliance includes, for example, a silicon catheter, a prosthetic foot, a prosthetic hand, a surgery glove, artificial skin, an artificial kidney, an artificial articulation, an artificial bone, a blood bag, a tube, a syringe, and an artificial tooth, but it is not limited thereto.

The anti-microbial or anti-coagulating medical appliance prepared by the method of the present invention has a maximum release speed of pharmaceutically active material, for example an anti-microbial, of 10 ppm/100 hrs in an aqueous solution, and more preferably a maximum speed of 5 ppm/100 hrs.

In addition, according to the present invention, paint can be prepared by mixing a polymer resin and at least one kind of the anti-microbial and additive. The polymer resin is selected from a group consisting of alkyd resin, acryl resin, urethane resin, epoxy resin, phenol

resin, urea resin, melamine resin, and a modified resin thereof; and the additive is selected from hydroxypropylacrylate, 1,6-hexanedioldiacrylate, pentaerythritoltriacylate, or polyethylenedipentaerythritol. If required, commonly used additives such as a pigment, a diluent, a physical property
5 controlling monomer and oligomer, a polyol (e.g., acryl polyol, urethane polyol, epoxy polyol, urea-melamine polyol, etc.), etc. can be further added to the liquid resin composition. As the physical property controlling monomer, one or more kinds selected from a group consisting of hydroxypropylacrylate (HPA), 1,6-hexandioldiacrylate (HDDA),
10 pentaerythritol triacylate (PETA), polyethylenglycoldiacrylate (PEGDA), trimethylolpropane ethoxylate triacylate (TMPEOTA), and dipentaerythritol hexaacylate (DPHA) can be used.

The anti-microbial and commonly used resin composition can be used as a coating agent, and natural curing, heat-curing, UV curing
15 treatment, etc. can be involved.

The present invention will be explained with reference to the following Examples, but they are to illustrate the present invention and the present invention is not limited to them.

EXAMPLES

20 Example 1

Preparation of anti-microbial polymer resins and anti-microbial tests

As an anti-microbial agent, norfloxacin and ciprofloxacin chlorate (hereinafter referred to as 'ciprofloxacin'), pipemidic acid, and enoxacin
25 were added to and mixed with a commonly used resin with the composition

as shown in the following Table 1, and zinc stearate as a heat stabilizer and paraffin wax and E.B.S. as a dispersant were added and all compounds were mixed in a high speed mixer. The composition was manufactured into a sample of a size of 4.5 x 7.0 cm while changing the
5 temperature from 100 to 300 °C using a preexisting injection molding apparatus. The bacterial decrease rate was measured according to a shake flask method using *E.coli* (KCTC 1682) as a host, of which results are as shown in the following Table 1.

[Table 1]

		PP	LLDPE	LDPE	HDPE	ABS	SAN
Cipro-floxacin	5 (wt%)	95	95	95	95	95	95
	Bacteria decrease rate (%)	100	100	100	100	99.99	99.99
	1 (wt%)	99	99	99	99	99	99
	Bacteria decrease rate (%)	99.99	99.99	99.99	99.99	99.99	99.99
Nor-floxacin	5 (wt%)	95	95	95	95	95	95
	Bacteria decrease rate(%)	100	100	100	100	99.99	99.99
	1(wt%)	99	99	99	99	99	99
	Bacteria decrease rate(%)	99.99	99.99	99.99	99.99	99.99	99.99
Pipemidic acid	5(wt%)	95	95	95	95	95	95
	Bacteria decrease rate (%)	99.99	99.99	99.99	99.99	99.97	99.97
	1 (wt%)	99	99	99	99	99	99
	Bacteria decrease rate (%)	99.95	99.97	99.96	99.89	99.95	99.93
Enoxacin	5 (wt%)	95	95	95	95	95	95
	Bacteria decrease rate (%)	100	100	100	100	99.99	99.99
	1 (wt%)	99	99	99	99	99	99
	Bacteria decrease rate (%)	99.99	99.99	99.99	99.99	99.96	99.94

Each commonly used resin (PP, LLDPE, LDPE, HDPE, ABS, SAN) comprised 0.2 wt% of zinc stearate, 0.2 wt% of paraffin wax and 0.25 wt%

5 of E.B.S.

Example 2

Preparation of anti-microbial master batches and anti-microbial tests

A known anti-microbial, a commercialized commonly used LLDPE
5 resin, a dispersant, and an antioxidant were introduced into a high speed
mixer, they were stirred at a high speed for about 30 minutes to mix, and
then extrusion molded in an extrusion molding apparatus at a molding
temperature of 170 to 210 °C to prepare an anti-microbial master batch in
a pellet form. Each anti-microbial master batch or compound was
10 prepared using HDPE and PP by the same method. Each compositional
ratio is as shown in Table 2. Anti-microbial tests were conducted by the
shake flask method, of which results are described in Table 3.

[Table 2] Composition of anti-microbial master batches

	Pharmaceutically active material (wt%)	LLDPE ¹⁾	HDPE ²⁾	PP ³⁾	Dispers ant /lubrican t ⁴⁾	Antioxid ant ⁵⁾	Dispers ant ⁶⁾	Total (wt%)
Composi tion1	Ciprofloxacin 5	82.9	-	-	2	0.1	10	100
Composi tion2	Norfloxacin 5	-	82.9	-	2	0.1	10	100
Composi tion3	Enoxacin 5	-	-	83.4	1.5	0.1	10	100
Composi tion4	Pipemidic acid 5	82.9	-	-	2	0.1	10	100
Composi tion5	Clinafloxacin 5	-	82.9	-	2	0.1	10	100
Composi tion6	Grepafloxacin 5	-	-	82.9	2	0.1	10	100
Composi tion7	Lemefloxacin 5	82.9	-	-	2	0.1	10	100
Composi tion8	Sparfloxacin 5	-	82.9	-	2	0.1	10	100
Composi tion9	Temafloxacin 5	-	-	82.9	2	0.1	10	100
Composi tion10	Tosufloxacin 5	82.9	-	-	2	0.1	10	100
Composi tion11	Ciprofloxacin 5 + norfloxacin 5	77.9	-	-	2	0.1	10	100

note) 1) SK Co. Ltd. Product name CA 110

2) SK Co. Ltd.

Product name JH 910

3) product name H360F 4) N,N'-ethylene bis stearamide (E.B.S)

5) n-octadecyl-3(3'-5'-di-t-butyl-4-hydroxyphenyl)propionate

6) polyethylene wax

[Table 3] Anti-microbial test for anti-microbial master batches

5

(unit:%)

	E. coli (KCTC 1682)	S. aureus (KCTC 1621)	S. typhimurium (KCTC 1925)	P. aeruginosa (KCTC 2004)
Composition 1	99.99	99.99	99.99	99.99
Composition 2	99.99	99.99	99.99	99.99
Composition 3	99.99	99.99	99.99	99.99
Composition 4	99.99	99.99	99.99	99.99
Composition 5	99.99	99.99	99.99	99.99
Composition 6	99.99	99.99	99.99	99.99
Composition 7	99.99	99.99	99.99	99.99
Composition 8	99.99	99.99	99.99	99.99
Composition 9	99.99	99.99	99.99	99.99
Composition 10	99.99	99.99	99.99	99.99
Composition 11	99.99	99.99	99.99	99.99

Example 3

Preparation of anti-microbial master batches

Anti-microbial master batches with the compositions as shown in Table 4 were prepared by finely powdering one or two components of

ciprofloxacin, pipemidic acid, terbinafin chloric acid (hereinafter referred to as 'terbinafin') and miconazole, by the same method as in Example 2, and anti-microbial tests were conducted. The results are as described in Table 5. As a dispersant, N,N'-ethylene bis stearamide (E.B.S.) and polyethylene wax were used, and as an antioxidant, n-octadecyl-3(3'5'-di-t-butyl-4-hydroxyphenyl)propionate) was used.

[Table 4] Compositions of anti-microbial master batches

	LLDP E	Ciproflo xacin	Pipemi dic acid	Terbina fin	Micon azole	Dispers ant/lubri cant	Anti- oxidant	Dispers ant	Total (wt%)
Compositi on 12	84.9	1	-	2	-	2	0.1	10	100
Compositi on 13	84.9	1	-	-	2	2	0.1	10	100
Compositi on 14	82.2	-	1	2	-	1.5	0.3	13	100
Compositi on 15	82.2	-	1	-	2	1.5	0.3	13	100

[Table 5] Anti-microbial test for anti-microbial master batch

	Strain	Composition 12	Compositio n 13	Compositi on 14	Compositio n 15
Anti- microbial ¹⁾ (억제환)	E.coli(KCTC 1682)	8mm±1mm	9mm±1mm	8mm±1mm	10mm±1mm
	S.typhimurium (KCTC 1925)	11mm±1mm	11mm±1mm	10mm±1mm	10mm±1mm
	S. aureus (KCTC 1621)	9mm±1mm	8mm±1mm	8mm±1mm	7mm±1mm
Anti-fungi ²⁾	C. albicans (KCTC 7729)	0 grade	0 grade	0 grade	0 grade
	A. flavus (KCTC 6961)	0 grade	0 grade	0 grade	0 grade
Anti-pollutant ³⁾		Pass	pass	pass	Pass

Note) 1) measured by ASTM G22

2) measured by ASTM G21

Grade: 0 grade – Mold did not grow on a sample.

5 1 grade – Mold grew within 10% on a sample.

2 grade – Mold grew 10 to 30 % on a sample.

3 grade – Mold grew 30 to 60% on a sample.

4 grade – Mold grew 60% or more on a sample.

Example 4

10 Preparation of anti-microbial films using anti-microbial master batch

Anti-microbial packaging films were prepared by adding the anti-microbial master batch of Composition 1 of Example 2 respectively to LDPE and CPP in an amount of 5%. Anti-microbial tests were conducted by ASTM G22. As a control, common LDPE and CPP films to which the anti-microbial master batch was not added were used. The results are as

15

described in Table 6.

[Table 6] Anti-microbial test for anti-microbial film

		E. coli (KCTC 1682)	S. typhimurium (KCTC 1925)	K. pneumoniae (KCTC 1621)
Control	LDPE	0mm	0mm	0mm
Example 4-1		6mm±1mm	11mm±1mm	9mm±1mm
Control	CPP	0mm	0mm	0mm
Example 4-2		8mm±1mm	13mm±1mm	10mm±1mm

Example 5

5 Preparation of anti-microbial cutting boards

Anti-microbial cutting boards with a size of 24cm x 40 cm were prepared by respectively adding 1 wt%, 3 wt%, and 5 wt% of the anti-microbial master batches of Composition 1 of Example 2 to high density polyethylene (HDPE) resin. Injection molding was conducted at 170 to 210 °C. In order to confirm durability of anti-microbial effects, after leaving the boards in flowing tap water for 30 days, anti-microbial effects before and after were compared. Results are as described in Table 7 (ASTM G22).

[Table 7] Anti-microbial test for anti-microbial cutting boards

	1 wt% add		3 wt% add		5 wt% add	
	initial	After 30 days	initial	After 30 days	initial	After 30 days
E. coli (KCTC 1682)	2.5mm±1m m	2.0mm±1m m	5.5mm±1m m	5.0mm±1m m	5.2mm±1m m	5.1mm±1m m
S. typhimurium (KCTC 1925)	3.5mm±1m m	3.0mm±1m m	7.0mm±1m m	6.5mm±1m m	7.5mm±1m m	7.2mm±1m m

Example 6

Preparation of anti-microbial foly catheters and anti-microbial test

5 Anti-microbial foly catheters in the form of tubes were prepared by roll mixing a silicon resin, ciprofloxacin, and a catalyst with the composition of Table 8 for 30 to 60 minutes in an extrusion molding apparatus. Molding was conducted at 450 to 600 °C/5 sec. The molded products were cured for 2 hours while maintaining them at 200 °C in a drier to

10 remove remaining solvent. Anti-microbial test results are as described in Table 9. Anti-microbial effects were measured by ASTM G22 (measuring inhibited circle).

[Table 8] Compositions of anti-microbial foley catheters

	Peroxide catalyst	Pt catalyst	ciprofloxacin	Silicon resin	Total (wt%)
Composition 16	-	0.2	0.3	99.5	100
Composition 17	0.2	-	0.1	99.7	100
Composition 18	0.2	-	0.3	99.5	100
Composition 19	0.2%	-	1.0	98.8	100
Composition 20	0.2	-	3.0	96.8	100
Composition 21	0.2	-	5.0	94.8	100

[Table 9] Anti-microbial test for anti-microbial foley catheters

	S. aureus (AATC 1621)	E.coli (AATC 1682)	P. aeruginosa (AATC 2004)
Composition 16	2.0±0.1mm	0.5±0.1mm	1.0±0.1mm
Composition 17	2.0±0.1mm	0.5±0.1mm	1.0±0.1mm
Composition 18	2.0±0.1mm	2.0±0.1mm	1.5±0.1mm
Composition 19	6.0±0.1mm	7.5±0.1mm	6.5±0.1mm
Composition 20	14.0±0.1mm	10.0±0.1mm	7.5±0.1mm
Composition 21	14.0±0.1mm	10.5±0.1mm	7.5±0.1mm

5

Example 7

Preparation of anti-microbial silicon prosthetic feet and anti-microbial test

Anti-microbial prosthetic feet were prepared by roll mixing silicon

resin and ciprofloxacin with the compositions of Table 10 respectively for 2 hours, introducing it into a mold to reflux for 1 hour while maintaining it at 160°C, and then cooling to room temperature. Anti-microbial performance was examined by measuring the bacteria decrease rate using the shake
 5 flask method. Results are as described in Table 11.

1) Shake flask method conditions:

Test bacterial fluid was shaken at 25 °C 150 times/min.

2) Bacteria decrease rate was measured by the following Equation
 1.

10 [Equation 1]

Decrease rate = (number of bacteria in blank after 24 hours – number of bacteria in sample after 24 hours)/ (number of bacteria in blank after 24 hours – number of bacteria) x 100

[Table 10] Compositions of anti-microbial prosthetic feet

	ciprofloxacin	Silicon resin	Total (wt%)
Composition 22	1.0	99.0	100
Composition 23	3.0	97.0	100
Composition 24	5.0	95.0	100
Composition 25	10	90.0	100

15

[Table 11] Anti-microbial test for anti-microbial silicon prosthetic feet.

		Number of bacteria		
		Immediately after inoculation	After 24 hours	Decrease rate (%)
S. aureus (ATCC 6538)	Blank	5.0×10^5	683×10^9	-
	composition 22	5.0×10^5	0	100
	composition 23	5.0×10^5	0	100
	composition 24	5.0×10^5	0	100
	composition 25	5.0×10^5	0	100
P. aeruginosa (ATCC27853)	Blank	5.0×10^5	1.72×10^{10}	-
	composition 22	5.0×10^5	6.0×10^2	99.99
	composition 23	5.0×10^5	0	100
	composition 24	5.0×10^5	0	100
	composition 25	5.0×10^5	0	100

Example 8

Preparation of anti-microbial or anti-coagulating master batches

5 and anti-microbial or anti-coagulating test

Medical master batches with the compositions of Table 12 were prepared by adding 2 components of warfarin, ticlopidine, and clopidogrel,

which are known anti-microbial and anti-coagulating materials, to polyurethane (PU) resin, polypropylene (PP) resin, or linear low density polyethylene (LLDPE), which are commonly used medical polymer resins, in a non-solvent process. Anti-microbial effects were examined by the shake flask method, and the results are as described in Table 13.

[Table 12] Compositions of anti-microbial and anti-coagulating master batches

	Pharmaceutically active material (wt%)	PU	PP	LLDPE	total (wt%)
Composition 26	Warfarin 5	95	-	-	100
Composition 27	Warfarin 5	-	95	-	100
Composition 28	Warfarin 5	-	-	95	100
Composition 29	Ciprofloxacin 5 + warfarin 5	90	-	-	100
Composition 30	Ciprofloxacin 5 + clopidogrel 5	-	90	-	100
Composition 31	Ciprofloxacin 5 + ticlopidine 5	-	-	90	100
Composition 32	Norfloxacin 5 + clopidogrel 5	90	-	-	100
Composition 33	Norfloxacin 5 + warfarin 5	-	90	-	100
Composition 34	Norfloxacin 5 + ticlopidine 5	-	-	90	100

Note) Each resin (PU, PP, LLDPE) comprised 0.2 wt% of zinc stearate, 0.2 wt% of paraffin wax, and 25 wt% of E.B.S.

[Table 13] Anti-microbial test for anti-microbial or anti-coagulating master batches

	E.coli (KCTC 1682)	S. aureus (KCTC 1621)	S. typhimurium (KCTC 1925)	B. subtilis (KCTC 1021)	K. pneumoniae (KCTC 2690)
Composition n 26	0	0	0	0	0
Composition n 27	0	0	0	0	0
Composition n 28	0	0	0	0	0
Composition n 29	99.99	99.99	99.99	99.99	99.99
Composition n 30	99.99	99.99	99.99	99.99	99.99
Composition n 31	99.99	99.99	99.99	99.99	99.99
Composition n 32	99.99	99.99	99.99	99.99	99.99
Composition n 33	99.99	99.99	99.99	99.99	99.99
Composition n 34	99.99	99.99	99.99	99.99	99.99

Anti-coagulation test for anti-microbial or anti-coagulating master batches

5 A Sprague-Dawley rat (Korean Biolink) with a body weight of 250 to 300 g was etherized, and then 3.6 ml of blood was taken with a 25 ml syringe by a heart perforation method. In order to inhibit blood coagulation, 0.4 ml of 3.8% sodium citrate was previously introduced into the syringe, and the blood taken was instantly used for the test.

10 The master batches (M/B) of Compositions 26 to 34 and a control

master batch that did not contain pharmaceutically active material were respectively immersed in the rat blood solution, and then after 1 hour, anti-coagulation effects were compared. Results are as described in Table 14.

[Table 14]

	After 20 minutes	After 40 minutes	After 60 minutes
Control PU	+	++	+++
Control PP	+	++	+++
Control LLDPE	+	++	+++
Composition 26	-	+	+
Composition 27	-	+	+
Composition 28	-	+	+
Composition 29	-	+	+
Composition 30	-	+	+
Composition 31	-	+	+
Composition 32	-	+	+
Composition 33	-	+	+
Composition 34	-	+	+

5 Note)

+++ : Surface blood coagulation seriously appeared.

++ : Surface blood coagulation appeared.

+ : Surface blood coagulation slightly appeared.

- : No surface blood coagulation appeared

10 Control PU, PP, and PE master batches showed serious blood aggregation after 1 hour, while master batches comprising the anti-coagulant showed delayed blood coagulation. As can be seen from the results of Tables 13 and 14, anti-microbial and anti-coagulation effects were maintained even after molding processing.

Example 9

Preparation of anti-microbial or anti-coagulating polyurethane (PU) catheters and anti-microbial or anti-coagulation test

Anti-microbial or anti-coagulating polyurethane catheters were prepared by roll mixing anti-microbial ciprofloxacin and norfloxacin and anti-coagulant norfloxacin with medical polyurethane (PU) with the compositions of Table 15, introducing it into a mold to reflux for 1 hour while maintaining it at 160 °C, and then cooling to room temperature. Anti-microbial performance was examined by the shake flask method, and the results are described in Table 16. Anti-coagulation performance results are as described in Table 17.

[Table 15] Compositions of anti-microbial or anti-coagulating polyurethane

	Anti-coagulant	Anti-microbial	Polyurethane resin	Total (wt%)
Composition 35	-	ciprofloxacin 3.0	97.0	100
Composition 36	-	norfloxacin 3.0	97.0	100
Composition 37	Warfarin 3	-	97.0	100
Composition 38	Warfarin 3	-	97.0	100
Composition 39	Warfarin 3	ciprofloxacin 3.0	94.0	100
composition 40	Warfarin 3	norfloxacin 3.0	94.0	100

[Table 16] Anti-microbial test for anti-microbial or anti-coagulating polyurethane catheter

	S. aureus (AATC 1621)	E. coli (AATC 1682)	P. aeruginosa (AATC 2004)
Composition 35	99.99	99.99	99.99
Composition 36	99.99	99.99	99.99
Composition 37	0	0	0
Composition 38	0	0	0
Composition 39	99.99	99.99	99.99
Composition 40	99.99	99.99	99.99

Anti-coagulating tests for anti-microbial or anti-coagulating polyurethane catheters were conducted by the same method as in Example 8. The polyurethane catheter samples of Compositions 35 to 40 and the polyurethane catheter that did not comprise a pharmaceutically active material were immersed in the rat blood solution, and after 1 hour, anti-coagulating effects were compared. The results are as described in Table 17

[Table 17] Anti-coagulating test for anti-microbial or anti-coagulating polyurethane catheter

	After 20 min.	After 40 min.	After 60 min.
Control PU	+	++	+++
Composition 35	+	++	+++
Composition 36	+	++	+++
Composition 37	-	+	+
Composition 38	-	+	+
Composition 39	-	+	+
Composition 40	-	+	+

The control polyurethane (PU) catheter and catheters that did not contain anti-coagulant showed serious blood aggregation after 1 hour, while the polyurethane catheter containing anti-coagulant showed delayed blood coagulation. As can be seen from the results of Tables 16 and 17, anti-microbial or anti-coagulating effects are maintained even after molding processing.

Example 10

Anti-microbial polyurethane prosthetic feet and anti-microbial test

Anti-microbial polyurethane prosthetic feet were prepared by roll mixing medical polyurethane resin with anti-microbial materials with the compositions of Table 18 for 2 hours, introducing it into a mold to reflux for 1 hour while maintaining it at 160 °C, and then cooling to room temperature. Anti-microbial performance was examined by the shake flask method, and the results are described in Table 19.

[Table 18] Compositions of anti-microbial polyurethane prosthetic feet

	Anti-microbial	Polyurethane resin	Total (wt%)
Composition 41	Ciprofloxacin 2.5	97.5	100
Composition 42	clinafloxacin 2.5	97.5	100
Composition 43	enoxacin 2.5	97.5	100
Composition 44	grepafloxacin 2.5	97.5	100
Composition 45	lomefloxacin 2.5	97.5	100
Composition 46	norfloxacin 2.5	97.5	100
Composition 47	Pipemidic acid 2.5	97.5	100
Composition 48	sparfloxacin 2.5	97.5	100
Composition 49	temafloxacin 2.5	97.5	100
Composition 50	tosufloxacin 2.5	97.5	100

[Table 19] Anti-microbial test for anti-microbial polyurethane prosthetic feet

	S. aureus (AATC 1621)	E.coli (AATC 1682)	P. aeruginosa (AATC 2004)
Composition 41	99.99	99.99	99.99
Composition 42	99.99	99.99	99.99
Composition 43	99.99	99.99	99.99
Composition 44	99.99	99.99	99.99
Composition 45	99.99	99.99	99.99
Composition 46	99.99	99.99	99.99
Composition 47	99.99	99.99	99.99
Composition 48	99.99	99.99	99.99
Composition 49	99.99	99.99	99.99
Composition 50	99.99	99.99	99.99

Example 11

5 Preparation of anti-microbial gloves and anti-microbial test

Medical gloves were prepared by mixing medical PVC resin with anti-microbials with the compositions of Table 20, and compressing them into films. Anti-microbial performance was examined by the shake flask method, and the results are as described in Table 21.

[Table 20] Compositions of anti-microbial medical gloves

	Pharmaceutically active material	PVC resin	Total (wt%)
Composition 51	Ciprofloxacin 2.5	97.5	100
Composition 52	clinafloxacin 2.5	97.5	100
Composition 53	enoxacin 2.5	97.5	100
Composition 54	grepafloxacin 2.5	97.5	100
Composition 55	lomefloxacin 2.5	97.5	100
Composition 56	norfloxacin 2.5	97.5	100
Composition 57	Pipemidic acid 2.5	97.5	100
Composition 58	sparfloxacin 2.5	97.5	100
Composition 59	temafloxacin 2.5	97.5	100
Composition 60	tosufloxacin 2.5	97.5	100

[Table 21] Anti-microbial test for anti-microbial gloves

	S. aureus (AATC 1621)	E.coli (AATC 1682)	P. aeruginosa (AATC 2004)
Composition 51	99.99	99.99	99.99
Composition 52	99.99	99.99	99.99
Composition 53	99.99	99.99	99.99
Composition 54	99.99	99.99	99.99
Composition 55	99.99	99.99	99.99
Composition 56	99.99	99.99	99.99
Composition 57	99.99	99.99	99.99
Composition 58	99.99	99.99	99.99
Composition 59	99.99	99.99	99.99
Composition 60	99.99	99.99	99.99

Example 12

Preparation of anti-microbial liquid polymer resin compositions

One or two kinds of the anti-microbials ciprofloxacin and
 5 norfloxacin, and the anti-fungi/anti-pollutants ketoconazole and fluconazole,
 were finely powdered. The anti-microbials were slowly introduced into a
 mixer containing a liquid phase resin at room temperature while stirring at a
 high speed to uniformly mix them to prepare a liquid anti-microbial resin
 composition with the compositions of Table 22 (unit: wt%).

[Table 22] Anti-microbial liquid polymer resin compositions

Anti-microbial	Epoxy resin ¹⁾	Urethane-acrylate resin ²⁾	Acryl-melamine resin ³⁾	Alkyd-melamine resin ⁴⁾	Acrylpolyol resin ⁵⁾
Ciprofloxacin 1	99	99	99	99	99
Norfloxacin 1	99	99	99	99	99
Ketoconazole 0.5	99.5	99.5	99.5	99.5	99.5
Norfloxacin 1+ fluconazole 0.5	98.5	98.5	98.5	98.5	98.5
Ciprofloxacin 1+ketoconazole 0.5	98.5	98.5	98.5	98.5	98.5

Note)

1) Samwha paint industry Co. Ltd., product SB-EE-400

2) Samwha paint industry Co. Ltd., product SB-V-100

5 3) Samwha paint industry Co. Ltd., product SB-MA-61

4) Samwha paint industry Co. Ltd., product SB-MA-20

5) Aekyung Chemical Co. Ltd., product BURNOK

Anti-microbial, anti-pollution and yellowing tests for anti-microbial liquid polymer resin

10 The anti-microbial liquid resins prepared in Examples 12 were respectively coated on a polyethylene sheet and an aluminum plate, and then each of them was naturally cured, thermally cured, or UV-cured. Anti-microbial, anti-pollution, and yellowing tests were conducted, and the results are as described in Table 23.

[Table 23] Curing conditions and anti-microbial, yellowing, and anti-pollution test results

	Composition	Composition 2 ²⁾	Composition 3 ³⁾	Composition 4 ⁴⁾
Curing method	natural	thermal	UV	natural
Drying condition	2 hrs (20 °C)	30 min. (150 °C 160 °C)	8m/min (high pressure mercury lamp 80W/cm 1 Lamp)	2 hrs (20 °C)
Thickness of dried film (μm)	40	40	20	40
Anti-fungi property ⁵⁾	4 grade	4 grade	4 grade	0 grade
Anti-microbial property ⁶⁾ (mm)	7	8.0	7.5	7
Yellowing ⁷⁾	pass	pass	pass	pass
Anti-polluting property ⁸⁾	-	-	pass	pass

Note)

5 1) ciprofloxacin 1wt% + epoxy resin 99 wt%

2) ciprofloxacin 1 wt% + (acryl + melamine resin) 99 wt%

3) norfloxacin 1 wt% + fluconazole 0.5 wt% + (urethane + acrylate resin)
98.5 wt%

4) ciprofloxacin 1 wt% + ketoconazole 0.5 wt% + epoxy resin 98.5 wt%

10 5) strain : P. citrinum KCTC 6990 (measured by ASTM G21)

Grade : 0 grade – No mold growth on a sample

1 grade – Mold grew within 10% on a sample

2 grade – Mold grew 10 to 30 % on a sample

3 grade – Mold grew 30 to 60 % on a sample.

4 grade – Mold grew 60 % or more on a sample.

5 6) strain and test method : E.coli, KCTC 1682 (ASTM G22 method)

7) yellowing test: measured by ASTM D1925

8) Anti-pollution test: measured by ASTM D5589

Experiment 1

Measurement of environmental hormone of medical anti-microbial

10 polymer resin

For the material of the medical appliances of the Examples, whether or not environmental hormone exists was examined by the EPA 8270 method using a GC/MS analyzing apparatus (Shimadzu QP5050A). The results are as described in Table 24.

[Table 24] Test results for detection of environmental hormone

Environmental hormone	Master batch			Catheter,		Prosthetic feet	
	Composition 1	Composition 2	Composition 3	Composition 19	Composition 20	Composition 23	Composition 41
Diethylphthalate	x	x	x	x	x	x	x
Di-n-propyl	x	x	x	x	x	x	x
Phthalate	x	x	x	x	x	x	x
Di-n-butyl phthalate	x	x	x	x	x	x	x
Di-n-pentyl phthalate	x	x	x	x	x	x	x
Di-2-ethylhexyl phthalate	x	x	x	x	x	x	x
N-butyl benzyl phthalate	x	x	x	x	x	x	x
Di-2-ethylhexyl adipate	x	x	x	x	x	x	x
4-pentyl phenol	x	x	x	x	x	x	x
4-octyl phenol	x	x	x	x	x	x	x
Nonyl phenol	x	x	x	x	x	x	x

Note) x : No detected environmental hormone ● : environmental hormone detected

5 As can be seen from the results of Table 24, no environmental hormone was detected from the master batches, catheters, or prosthetic feet, indicating that they are safe for medical appliances.

Experiment 2

Test for elution of anti-microbial material

For the material of the medical appliances/instruments of Examples,
an anti-microbial material elution test was conducted using distilled water
5 (DW) by KFDA 1999-18. The results are as described in Table 25.

[Table 25] Anti-microbial material elution test

	Master batch		Catheter,		Prosthetic feet
	Composition 1	Composition 2	Composition 19	Composition 20	Composition 41
Measurement of absorbance (250-350nm) : 0.1% or less	PASS	PASS	PASS	PASS	PASS
Non-volatile component: 1mg 이하	PASS (0.30mg)	PASS (0.28mg)	PASS (0.31mg)	PASS (0.27mg)	PASS (0.33mg)
Heavy metal contents : ND	ND	ND	ND	ND	ND
pH : 1.0 or less	0.33	0.29	0.35	0.32	0.41

Experiment 3

Measurement of released amount of anti-microbial or anti-
10 coagulating material

For LLDPE M/B respectively containing 5% and 10% of ciprofloxacin and 10% of warfarin, the released amounts of anti-microbial material were measured with passage of time. The results are as described in Table 26.

[Table 26] Measurement of released amount of anti-microbial or anti-coagulating material

	3hrs	48hrs	120hrs	240hrs	Elution test liquid
LLDPE M/B (containing 5% ciprofloxacin)	1.2ppm	1.5ppm	1.5ppm	1.5ppm continuous release	H ₂ O
LLDPE M/B (containing 10% ciprofloxacin)	2.5ppm	4ppm	5ppm	4ppm-5ppm continuous release	H ₂ O
LLDPE M/B (containing 10% warfarin)	0.9ppm	1.1ppm	1.2ppm	1.6ppm-1.9ppm continuous release	H ₂ O

As can be seen from Table 26, LLDPE polymer resin continuously released a maximum of 5 ppm of anti-microbial material, indicating that a rapid anti-microbial effect decrease can be prevented, thereby increasing anti-microbial effect durability. And, anti-coagulating material showed similar results. Such results can solve the toxic problem in a body due to excessive drug release.

As explained, the present invention mixes commonly used polymers such as silicon, urethane resin, etc. with pharmaceutically active materials that are safe to a human body by a simple addition method of non-solvent type instead of the preexisting method of coating an active material on the surface of a polymer after processing it using an organic solvent. Accordingly, mixing of a commonly used polymer resin and a pharmaceutically active material is superior without using a solvent, a superior anti-microbial effect can be maintained even after high temperature processing, and a toxic problem due to elution can be solved.

Therefore, anti-microbial or anti-coagulating properties can be imparted to industrial appliances, household appliances, petrochemicals such as an anti-polluting paint, and natural rubber, as well as to medical materials.

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